

**Remarks**

The Office Action mailed October 19, 2004 has been received and reviewed. Claims 1-46 having been canceled, claims 47, 52, and 53 having been amended, and claims 54-62 having been added, the pending claims are claims 47-62.

The specification has been amended at the paragraph spanning pages 10-11 to properly show two paragraphs, and the second paragraph has been amended to more clearly describe Figure 6. The specification has been amended at pages 41 and 44 to capitalize the trade designations recited for reagent kits. The specification has also been amended at pages 5-8, 11-12, and 17-20 to recite SEQ ID NOs.

Claim 47 has been amended for clarification to recite the sequence being crystallized. Claims 52 and 53 have been rewritten in independent form.

New claim 54 is supported, for example, by originally filed claims 48-50.

New claims 55-62 are directed to selected portions of a protein that include the identified binding sites. Specifically, the end points of the polypeptide recited in new claim 55 are supported, for example, by the first and last residues listed in Tables 2 to 4, at pages 5-7 of the specification. Thus the polypeptide recited in claims 55-58 includes the FAD binding site recited in originally filed claims 1-3. The end points of the polypeptide recited in new claim 59 are supported, for example, by the first and last residues listed in Tables 5 to 7 at page 8 of the specification. Thus the polypeptide recited in claims 59-62 includes the NADPH binding site recited in originally filed claims 4-6.

Reconsideration and withdrawal of the rejections are respectfully requested.

**Objection to the Specification**

The Examiner objected to the specification for allegedly using trademarks, which were not capitalized. While not taking a position on whether the trade designations of the screening solutions are trademarks, Applicant has amended the specification at pages 41 and 44

by capitalizing the trade designations of the reagent kits, and the objection has been rendered moot.

The Examiner also objected to the specification for allegedly reciting specific amino acid residues not identified by a sequence identification number. The specification having been amended at pages 5-8, 11-12, and 17-20 to recite SEQ ID NOs, Applicant respectfully submits that the objection has been rendered moot.

Applicant respectfully requests that the Examiner reconsider and withdraw the objection to the specification.

### **Objection to Drawings**

The Examiner objected to Figures 6a-6d, and alleged that the indicated figures did not illustrate what was intended. Applicant notes that the Examiner has not acknowledged receipt of the Replacement Drawings submitted by Applicant on December 28, 2001 (Figures 1-18) and February 12, 2002 (Figures 4a-4b). Applicant respectfully requests that the Examiner acknowledge and consider the Replacement Drawings submitted by Applicant. In the event that the Replacement Drawings have been misplaced, Applicant will resubmit the Replacement Drawings upon notification to that effect.

Applicant believes that the Replacement Drawings submitted on December 28, 2001 and February 12, 2002 are of acceptable quality, and respectfully requests that the Examiner specifically note any formalities therein. Applicant has also amended, herein, the *Brief Description of the Figures* in the specification to more clearly describe Figures 6a-6d.

As noted herein above regarding the Amendment to Figure 11, typographical errors for residues in SEQ ID NO:1 have been corrected to properly show residue 164 as "L" and residue 204 as "L." The amendment is supported, for example, by the residues in SEQ ID NO:1 in Figure 15, and the residues listed in Table 1. Accordingly, a substitute sequence listing is being submitted herewith in which SEQ ID NO:1 has been amended to correspond with Figure 15 and Figure 11 (as amended). No new matter has been added.

Reconsideration and withdrawal of the objection to the drawings are respectfully requested.

**Objection to the Claims**

The Examiner objected to claims 52 and 53 under 37 C.F.R. 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant respectfully disagrees. However, in the interest of expediting the prosecution of the present application, claims 52 and 53 have been rewritten in independent form, and the objection has been rendered moot.

Reconsideration and withdrawal of the objection is respectfully requested.

**Rejection under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claims 1-7 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 1-7 having been canceled, and the rejection has been rendered moot.

Reconsideration of the rejection under 35 U.S.C. §112, second paragraph, are respectfully requested.

**Rejection under 35 U.S.C. §101**

The Examiner rejected claims 1-7 under 35 U.S.C. 101 as being directed toward non-statutory subject matter. Claims 1-7 having been canceled, Applicant respectfully submits that the rejection has been rendered moot.

Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §101.

**Rejection under 35 U.S.C. §102**

The Examiner rejected claims 1-7 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,767,536 (Aharonowitz et al.). The Examiner also rejected 1, 4, and 7 under 35 U.S.C. 102(b) as being anticipated by or, in alternative, under 35 U.S.C. 103(a) as being unpatentable over Waksman et al., ("Crystal Structure of *Escherichia coli* Thioredoxin Reductase Refined at 2 Å Resolution. Implications For a Large Conformational Change During Catalysis," *J. Mol. Biol.*, 1994 Feb. 25; 236(3):800- 816). Claims 1-7 having been canceled herein, Applicant respectfully submit that the rejection has been rendered moot.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §§102 and/or 103 are respectfully requested.

**Rejection under 35 U.S.C. §112, First Paragraph**

**WRITTEN DESCRIPTION**

The Examiner rejected claims 7 and 47-53 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 7 has been canceled. Applicant respectfully traverses the rejection of claims 47-53.

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." M.P.E.P. §2163. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Claim 47 (as amended) is directed to a method for crystallizing *S. aureus* thioredoxin reductase; and claims 48-53 (as amended) are directed to crystals of *S. aureus* thioredoxin reductase.

Applicant respectfully submits that the specification (including, for example, the originally filed claims) provides an adequate written description for methods for crystallizing *S. aureus* thioredoxin reductase. For example, method claim 47 (as amended) recites that the amino acid sequence of the *S. aureus* thioredoxin reductase comprises SEQ ID NO:1 (e.g., Figures 11 and 15), or SEQ ID NO:1, except that at least one methionine is replaced with selenomethionine (e.g., page 38, line 27 to page 41, line 2; page 41, line 15 to page 44, line 9; and page 45, lines 8-31). Method claim 47 (as amended) further recites appropriate crystallization conditions including, for example, concentration of the *S. aureus* thioredoxin reductase (e.g., page 2, lines 24-25) and solution description: e.g., pH of about 6 to about 10 (e.g., page 13, line 4); about 100 mM to about 6 M sodium formate (e.g., page 13, line 5); and optionally up to about 40 wt. % DMSO (e.g., page 13, line 6). Thus, Applicant respectfully submits that the specification, which includes the originally filed claims, adequately supports a method for crystallizing *S. aureus* thioredoxin reductase (e.g., claim 47).

Further, Applicant respectfully submits that the specification (including, for example, the originally filed claims) provides an adequate written description for crystals of *S. aureus* thioredoxin reductase (e.g., claims 48-53, as amended). The crystal claims recite various parameters including, for example, space group symmetry (e.g., claim 49; and page 12, line 27), unit cell dimensions (e.g., claim 50; and page 12, lines 28-30), structure coordinates (e.g., claim 51; structure coordinates in Table 1; and description of structure at page 14, line 15 to page 19, line 2), and amino acid sequence (e.g., claims 52-53, as amended; Figures 11 and 15; page 38, line 27 to page 41, line 2; page 41, line 15 to page 44, line 9; and page 45, lines 8-31). Thus, Applicant respectfully submits that the specification adequately supports crystals of *S. aureus* thioredoxin reductase (e.g., claims 48-53, as amended).

Moreover, Trilateral Project WM4 on *Comparative study on "protein 3-dimensional (3-D) structure related claims*, in referring to a hypothetical claim (i.e., "A crystalline form of protein P having unit cell dimensions of  $a=4.0\text{nm}$ ,  $b=7.8\text{nm}$ , and  $c=11.0\text{nm}$ ") stated that "[t]he claim complies with the written description requirement because the structure of protein P is provided." Trilateral Project WM4 on *Comparative study on "protein 3-dimensional (3-D) structure related claims*, Annex 3, Case 4, A3 ([http://www.uspto.gov/web/tws/wm4/pdf/wm4\\_3d\\_annex\\_3.pdf](http://www.uspto.gov/web/tws/wm4/pdf/wm4_3d_annex_3.pdf)). Applicant respectfully submits that the present specification provides the structure of *S. aureus* thioredoxin reductase. See, for example, the atomic structure coordinates listed in Table 1, and described, for example, at page 5, lines 5-16 of the specification.

Based on the remarks presented herein above, Applicant respectfully submits that the specification recites structural, physical, and chemical properties, along with a method of making the claimed invention, sufficient to satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

#### **ENABLEMENT**

The Examiner rejected claims 1-7 and 47-53 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1-7 have been canceled. Applicant respectfully traverses the rejection of claims 47-53.

"A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." M.P.E.P. §2164.04. "As long as the specification discloses at least one method for

making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied."

M.P.E.P. §2164.01(b). "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be *used* in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not *use* the genus as a whole without undue experimentation." M.P.E.P. §2164.02, paragraph entitled "WORKING EXAMPLES AND A CLAIMED GENUS" (emphasis added). "[E]ven in unpredictable arts, a disclosure of every operable species is not required." M.P.E.P. §2164.03.

Applicant further submits that claims 47-53 are fully enabled by the specification. Although not required, the specification includes working examples of methods for crystallizing *S. aureus* thioredoxin reductase (e.g., page 41, lines 4-18; and page 44, line 11 to page 45, line 6). The specification also provides methods of using the claimed crystals (e.g., homology modeling and rational drug design; page 29, line 23 to page 36, line 29). Moreover, the Examiner has not provided any reason to doubt the objective truth of the disclosure provided in the specification.

Moreover, Applicant respectfully submits that one of skill in the art, using the disclosure provided in the specification (including the working examples), would be able to make and use the entire scope of the invention as recited in claims 47-53. For example, Applicant's Representatives respectfully submit that the present disclosure of methods of making and using crystals of *S. aureus* thioredoxin reductase provides enablement for one of skill in the art, without undue experimentation, to make additional crystals of *S. aureus* thioredoxin reductase. For example, Applicant's Representatives respectfully submit that the presently disclosed crystals provide enablement for one of skill in the art to use the crystals in, for example, cross-seeding techniques to make additional crystals of *S. aureus* thioredoxin

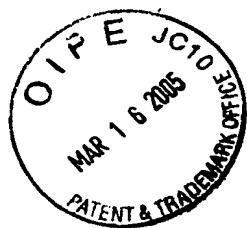
reductase. Thus, Applicant respectfully submits that claims 47-53 (as amended) are fully enabled by the specification.

Based on the remarks presented herein above, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

### **New Claims**

New claim 54 is directed to a crystal of *S. aureus* thioredoxin reductase. New claims 55-62 are directed to polypeptides consisting of a portion of *S. aureus* thioredoxin reductase. Applicant respectfully submits that claims 54-62 are patentable for at least the reasons discussed herein above for the patentability of claims 47-53. Entry and consideration of new claims 54-62 are respectfully requested.





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Annotated Sheet  
Showing Changes

SEQ ID NO:2	TrxB_ecoli	(1)	-GTTKHSKLLIIGSGPAGYTAAVYAARANLQPVLTITGMEKGGQTTTTEV	50
SEQ ID NO:1	TrxB_sa	(1)	MGTEIDDFDAIIGAGPAGMTAAVYAARANLKTVMIERGIPGGQMANTEEV	
	TrxB_ecoli	(50)	ENWPGDPNDLTGPLLMMRMHEHATKFEETIIEHDHINKVDELQNRPPFRINGD	100
	TrxB_sa	(51)	ENWPG-PFEMITGPDLSLTMFEEHAKKFGAVVQYGDIKSVHDKGEYKVTFNG	
	TrxB_ecoli	(100)	NGEYTCDAIIATGASARYNGPSPSEAFKGRGVSAACATCDGFFEVANQKVA	150
	TrxB_sa	(100)	NKELTAKAIIATGAEYKKIGVPGEQELGGRGVSYCAVCDGAFENKELF	
	TrxB_ecoli	(150)	VIGGNTAAVEEALMLNIASEVHETRRRDGFRAEKILIKRLMDKVENGNI	200
	TrxB_sa	(150)	VIGGDSAVEESTETPKFADKVTIVHRRDELRAQRILQDRAFKN---DKI	
	TrxB_ecoli	(200)	ILHTNRTTEMTGDQMGVTGVRRLRDTQNSDNIESLEVAGFFVAIGHSPNT	250
	TrxB_sa	(197)	DFIWSHTTKSINEKDGKVGSVTLTST-KDGESEETHEADGVFTYIGMKPLT	
	TrxB_ecoli	(250)	AFIEGQ-TELENGYIKVQSGIHGNATQTSIPGVFAAGDVMMDHIYRQATISA	300
	TrxB_sa	(246)	APFKDLGFTNEBVGVIIVTK--DD---MTTSVPGFFAAGDVRDKGLRQIVTAT	
	TrxB_ecoli	(300)	GTGMAALDAERYDDGLADAK-----	329
	TrxB_sa	(292)	GDGSAQAQSAAEYAEHLNDQARSHHHHHH	

*no under line*

Fig. 11